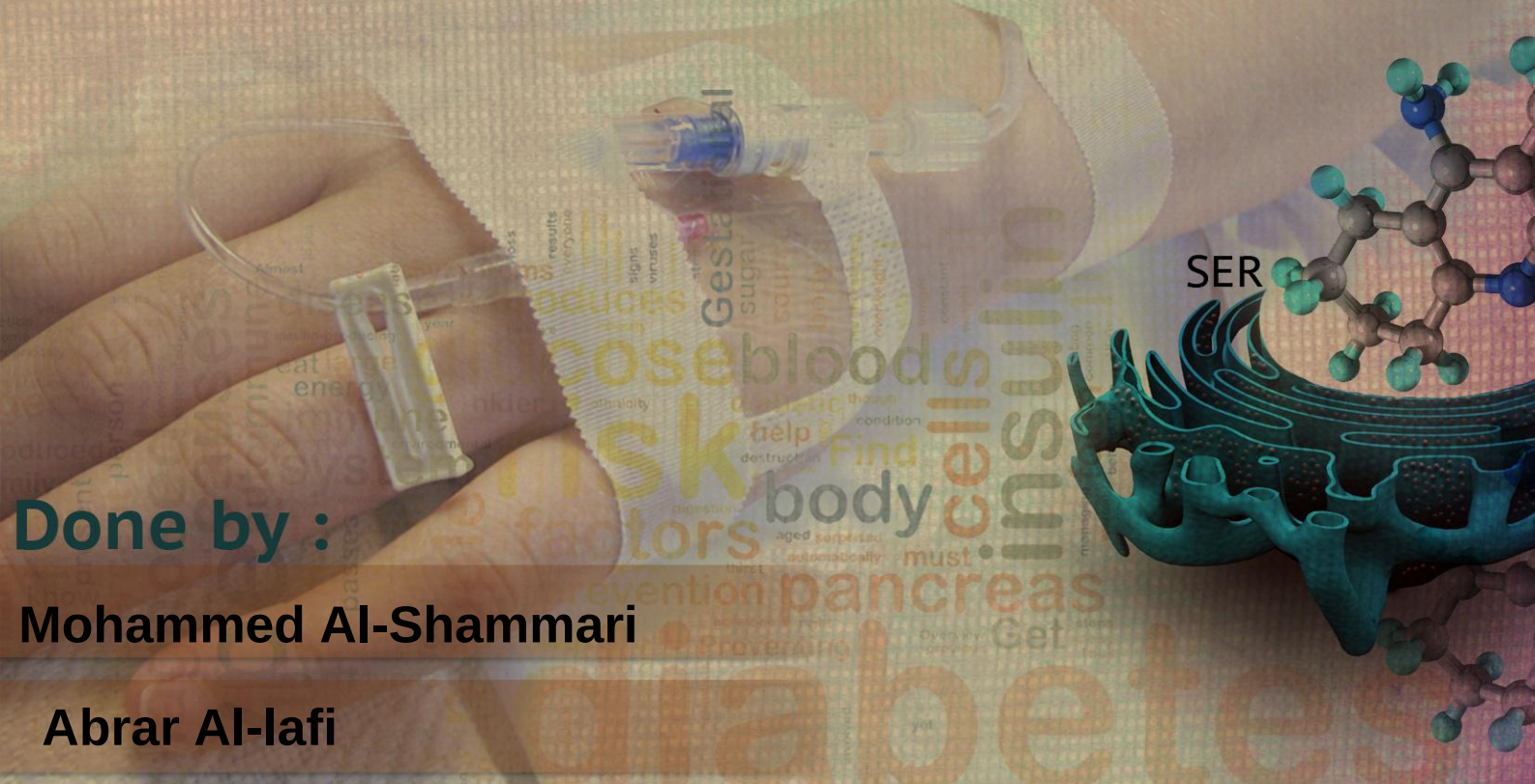
431 Teams
medical students

DT431 Team Pharmacology

Endocrine block

Lecture 8

Oral hypoglycemic drugs part I



Done by :

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Oral Hypoglycemic Drugs

Diabetes Mellitus :

- **Type I**

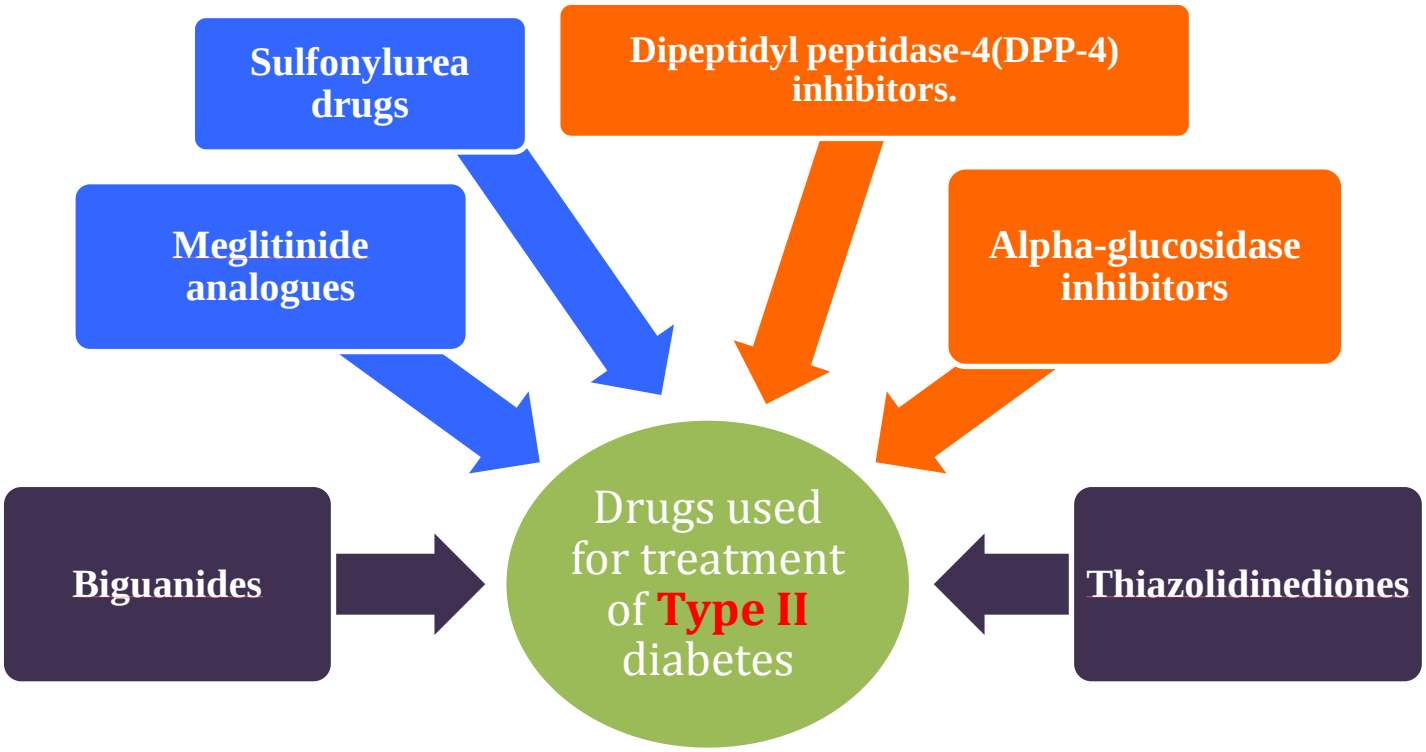
  due to autoimmune or viral diseases.

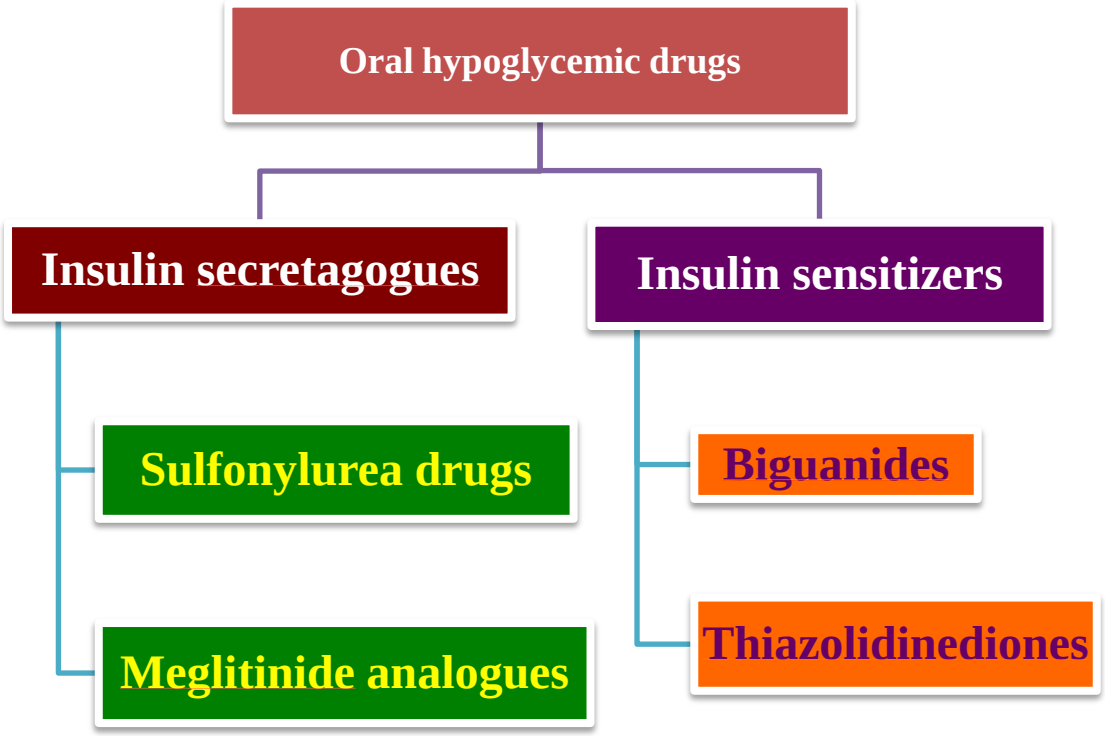
- **Type II**

  due to obesity, genetic factors.

- Patients with **Type II** they have 2 physiological defects:

1. Abnormal insulin secretion.
2. Resistance to insulin action in target tissues associated with decreased number of insulin receptors.

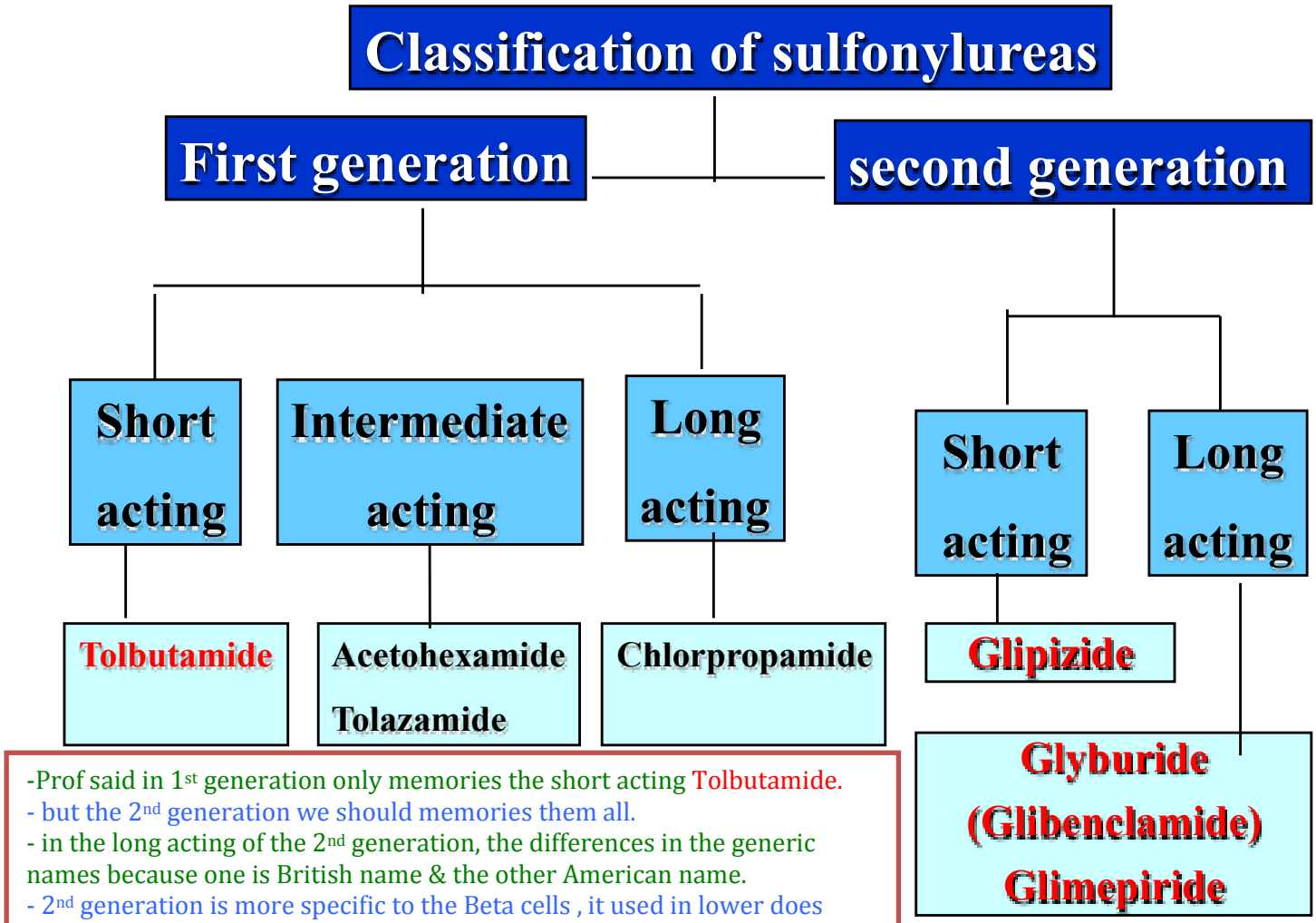




Insulin secretagogues:

Are drugs which increase the amount of insulin secreted by the pancreas, include:

1- sulfonylureas:



-Prof said in 1st generation only memories the short acting Tolbutamide.
- but the 2nd generation we should memories them all.
- in the long acting of the 2nd generation, the differences in the generic names because one is British name & the other American name.
- 2nd generation is more specific to the Beta cells , it used in lower does than 1st generation & has long action than 1st generation.
-2nd generation more potent than 1st generation
-2nd generation most commonly used now!

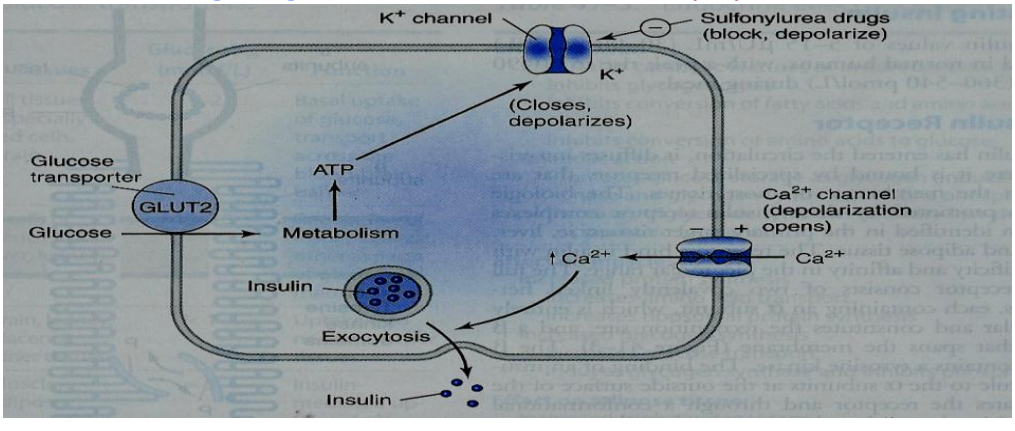
a. MOA of **Sulfonylureas**:

❖ The main mechanism:

- Stimulate insulin release from functioning B cells by blocking of ATP-sensitive K channels resulting in depolarization and calcium influx (Hence, not effective in totally insulin-deficient pts" type-1).

❖ Other proposed mechanisms:

- Potentiation of insulin action on target tissues.
- Reduction of serum glucagon concentration. "indirectly by increase insulin secretion"



Con't **sulfonylureas:**

b. Pharmacokinetics of **sulfonylureas**:

- Orally, well absorbed.
- Reach peak concentration after 2-4 hr.
- All are highly bound to plasma proteins.
- Duration of action is variable.
- Second generation has longer duration than first generation.
- Metabolized in liver
- excreted in urine , so we have to readjust the dose for elderly and in case of renal D
- Cross placenta, stimulate fetal B cells to release insulin → hypoglycemia at birth.

"so it's contraindicated in pregnant women, in pregnant we only give insulin"

First generation sulfonylurea

	Tolbutamid short-acting	Acetohexamide intermediate-acting	Tolazamide intermediate-acting	Chlorpropamide long- acting
Absorption	Well	Well	Slow	Well
Metabolism	Yes	Yes	Yes	Yes
Metabolites	Inactive	Active	Active	Inactive
Half-life	4 - 5 hrs	6 – 8 hrs	7 hrs	24 – 40 hrs
Duration of action	Short (6 – 8 hrs)	Intermediate (12 – 20 hrs)	Intermediate(12 – 18 hrs)	Long (20 – 60 hrs)
Excretion	Urine	Urine	Urine	Urine

prof said this table is not for memorizing, we should know that because the Tolbutamid is metabolized inactive so it's good for old diabetic patient or patient with renal impairment "bcoz in these patients the renal function is impaired so drug will stay longer in blood so if it metabolized inactive it's good" while the others as we see their metabolites are active so in pt. with renal impairment they will have long action which may lead to hypoglycemic coma.

Tolbutamide:

safe for old diabetic patients or patient with renal impairment.

Con't **sulfonylureas:**

Second generation sulfonylurea

	Glipizide	Glibenclamide (Glyburide) Used commonly	Glimepiride
Absorption	Well	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites	Inactive	Moderate activity	Moderate activity
Half-life	2 – 4 hrs	Less than 3 hrs	5 - 9 hrs
Duration of	10 – 16 hrs	12 – 24 hrs	12 – 24 hrs
action	short	long	long
Doses	Divided doses 30 min before meals	Single dose	Single dose 1 mg
Excretion	Urine	Urine	Urine

The 2nd generation has short half life &long duration "hit & run effect"
they make the B-cells release insulin & they disappear after short time ,but their effect in beta cells stay for longer time.

C. Uses of **sulfonylureas**:

Type II diabetes:

monotherapy or in combination with other anti-diabetic drugs.

D. Unwanted Effects of **sulfonylureas**:

- 1. Hyperinsulinemia & Hypoglycemia.(Any drug which acts as Insulin secretagogues Has hypoglycemic effect)

2. Weight gain due to increase in appetite "+ due to the anabolic action of insulin which is secreted"

2- Meglitinide analogues:

e.g. **Repaglinide**

Rapidly acting insulin secretagogues

a. MOA of Sulfonylureas:

same MOA of sulfonylureas

b. Pharmacokinetics of sulfonylureas:

- Orally, well absorbed.
- Very fast onset of action, peak 1 h.
- taken just before every meal because they have short duration of action (4 h)-."shorter than sulfonylureas, so less incidence of hypoglycemia than sulfonylureas "
- Metabolized in the liver & excreted in bile.

C. Uses of Meglitinide:

- **Type II diabetes**:
  monotherapy or combined with other antidiabetic drugs.
- Patients allergic to sulfonylurea.

D. side Effects of Meglitinide:

- Hypoglycemia
- Weight gain.

Insulin sensitizers:

1. Biguanides:

e.g. **Metformin**

a. MOA of Metformin:

- **Increases liver ,muscle & adipose tissues sensitivity to insulin & increase peripheral glucose utilization(glycolysis)**
- Inhibits gluconeogenesis.
- Impairs glucose absorption from GIT.
- **Does not stimulate insulin release and Does not require functioning *B* cells.**

b. Pharmacokinetics of Metformin:

- orally.
- Not bound to serum protein.
- Not metabolized.
- t 1⁄2 3 hours.
- Excreted unchanged in urine

c. Uses of Metformin:

- **Obese patients with type II diabetes.**
- Monotherapy or in combination.

+ it maybe used in Type I diabetes

d. Advantages of Metformin:

No risk of hyperinsulinemia or hypoglycemia or weight gain (anorexia).

e. side Effects of Metformin:

- Metallic taste in the mouth
- GIT disturbances: nausea, vomiting, diarrhea
- Lactic acidosis
- Long term use interferes with vitamin B12 absorption.

f. Contraindications of metformin:

- **Pregnancy**.
- Renal disease.
- Liver disease.
- Alcoholism.
- Heart failure

→ Because of increase risk of lactic acidosis.

Wiki:
http://en.wikipedia.org/wiki/Metformin#Lactic_acidosis

2- Thiazolidinediones (glitazones)

e.g **Pioglitazone**

a. MOA of Pioglitazone:

- **Activate PPAR-γ (peroxisome proliferator-activated receptor -γ).**
- **Increase sensitivity of target tissues to insulin.**
- Increase glucose uptake and utilization in muscle and adipose tissue.

b. Pharmacokinetics of Metformin:

- Orally (once daily dose).
- Highly bound to plasma albumins (99%).
- Slow onset of activity.
- Half life 3-4 h
- Metabolized in the liver.
- Excreted in urine 64% & bile..

c. Uses of pioglitazone:

"pioglitazone used when other OHC didn't show any response so we do NOT usually use it as 1st line because of its side effects"

- Type II diabetes with insulin resistance.
- Used either alone or combined with sulfonylurea, biguanides or insulin.
- No risk of hypoglycemia when used alone

d. Adverse effects of pioglitazone:

- **Hepatotoxicity ?? (liver function tests for 1st year of therapy).**
- **Fluid retention (Edema).**
- **Precipitate congestive heart failure**
- **Contraindicated in Pregnancy and Lactating women**
- **Mild weight gain.**

Thanks for 430 for the following summary and questions.

1-A 50-year-old woman has just been diagnosed withtype 2 diabetes and given a prescription for metformin.
Which of the following statements is characteristic of this medication?
A. Metformin is inappropriate for initial management of type 2 diabetes.
B. Metformin decreases hepatic glucose production.
C. Metformin undergoes significant metabolism via the cytochrome P450 system.
D. Metformin should not be combined with sulfonylureas or insulin.
E. Weight gain is a common adverse effect.

2-Which of the following classes of glucose-lowering agents has the ability to reduce insulin resistance?
A. α-glucosidase inhibitors.
B. DPP-IV inhibitors.
C. Meglitinides.
D. Sulfonylureas.
E. Thiazolidinediones.

3-A 64-year-old woman with a history of type 2 diabetes is diagnosed with heart failure. Which of the following medications would be a poor choice for controlling her diabetes?
A. Exenatide.
B. Glyburide.
C. Nateglinide.
D. Pioglitazone
E. Sitagliptin.

4-Which of the following drugs promotes the release of endogenous insulin?
A. Acarbose
B. Glipizide
C. Metformin
D. Miglitol
E. Pioglitazone

5-Which of the following is an important effect of insulin?

A. Incresed conversion of amino acids into glucose
B. Increased gluconeogenesis
C. Increased glucose transport into cells
D. Inhibition of of lipoprotein lipase
E. Stimulation of glycogenolysis

6-A 54 yr old obese patient with type 2 diabetes has a history of alcoholism. In this patient , metformin should either be avoided or used with extreme caution because the combination of metformin and ethanol increases the risk of which of the following?

A. A disulfiram-like reaction
B. Excessive weight gain
C. Hypoglycemia
D. Lactic Acidosis
E. Severe hepatotoxcity

7-Which of the following drugs is taken during the first part of a meal for the purpose of delaying the absorption of dietary carbohydrates?

A. Acarbose
B. Exenatide
C. Glipizide
D. Pioglitazone
E. Repaglinide

8- The PPAR-□ □receptor is activated by thiazolidinediones increase tissue sensitivity to isulin by which of the following mechanisms?

A. Activating adenylyl cyclase and increasing the intracellular concentration of cAMP
B. Regulates transcription of genes involoved in glucose utilization
C. Inhibit acid glucosidase, a key enzyme in glycogen breakdown pathway
D. Stimulate the activity of tyrosine kinase that phosphorylates the isulin recptor
.

Answer key: 1-B, 2-E, 3-D, 4-B, 5-C, 6-D, 7-A, 8- B